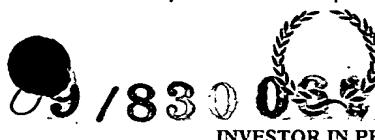




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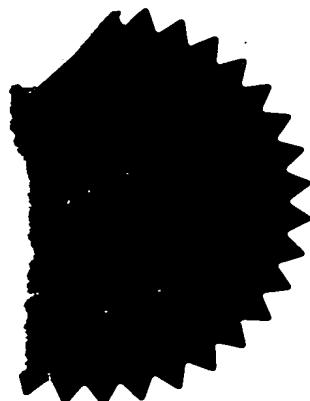
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each applicant *(underline all surnames)*  
GLAXO GROUP LIMITED  
GLAXO WELLCOME HOUSE  
BERKELEY AVENUE  
GREENFORD  
MIDDLESEX  
UB6 0NNPatents ADP number *(if you know it)*

673587003

If the applicant is a corporate body, give the  
country/state of its corporation4 Title of the invention FLUTICASONE LOTION HAVING IMPROVED  
VASOCONSTRICTOR ACTIVITY5 Name of your agent *(if you know one)*KAREN CRAWLEY  
(SEE CONTINUATION SHEET)"Address for service" in the United Kingdom  
to which all correspondence should be sent  
*(including the postcode)*GLAXO WELLCOME PLC  
GLAXO WELLCOME HOUSE, BERKELEY AVENUE  
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Request for preliminary examination and search (Patent Form 9/77)  
Request for substantive examination (Patent Form 10/77)  
Any other documents (please specify)

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11. I/We request the grant of a patent on the basis of this application

Signature: Karen Crawley 21 October 1998  
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom Kim Allen  
0181-966 5721

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## FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

### Background of the Invention

5

#### Field of the Invention

The present invention is directed to a fluticasone lotion having improved vasoconstrictor activity over a cream formulation. The fluticasone lotion exhibits 10 significant vasoconstrictor potency and excellent anti-inflammatory activity.

#### Description of Related Art

Fluticasone propionate is a steroid having anti-inflammatory, anti-pruritic, and 15 vasoconstrictive properties.

Fluticasone propionate cream (0.05%) is sold under the tradename Cutivate® cream. Each gram of Cutivate® cream (0.05%) contains 0.5 mg fluticasone propionate in a 20 base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, buffers and preservatives.

Mineral oil is a known occlusive agent. Occlusion in topical drug delivery is known to increase the vasoconstrictor potency of the topical steroid. By increasing the vasoconstrictor potency, the effectiveness of the steroid is increased. 25 Disadvantageously, occlusive agents such as mineral oil can reduce the esthetic appeal of topical formulations as they may impart an undesirable oily feel to the skin. With the removal or significant reduction of the occlusive agent, one of ordinary skill in the art would expect to see a decrease in the vasoconstrictor potency of the steroid, and thus a decrease in the effectiveness of the topical steroid formulation.

30

Surprisingly, it has been found by the present inventors that the removal of the occlusive agent actually increases the vasoconstrictor potency of fluticasone, and thus, the effectiveness of the steroid. Moreover, a lotion greatly improves the organoleptic feel and spreadability of the drug over a large area, when compared with 35 a cream. The present invention is based on the above finding.

Summary of the Invention

The present invention is directed to a topical fluticasone lotion for the treatment of dermatological disorders. The lotion comprises:

5

- (a) about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;
- (b) about 1.0 to about 10.0 wt.% of a C<sub>14</sub>-C<sub>20</sub> fatty alcohol, or mixtures thereof;
- (c) about 1.0 to about 5.0 wt.% of at least one skin conditioning agent; and

10 (d) about 5.0 to about 15.0 wt.% of propylene glycol; and up to about 10.0 wt.% mineral oil or soft white paraffin, and the balance being water which can contain additives such as preservatives and buffers.

This invention is also directed to a topical fluticasone lotion which comprises:

15

- (a) fluticasone propionate in an amount of from about 0.005 to about 1.0 wt.%;
- (b) a C<sub>14</sub>-C<sub>20</sub> fatty alcohol, or mixtures thereof, in an amount of from about 3.0 to about 7.0 wt.%;
- (c) at least one skin conditioning agent in an amount of from about 0.5 to about 3.0 wt.%;

20 (d) a surfactant in an amount of about 0.25 to about 3.0 wt.%;

- (e) propylene glycol in an amount of from about 7.0 to 12.0 wt.%; and
- (f) up to about 10 wt.% mineral oil or soft white paraffin.

Detailed Description of the Preferred Embodiments

25

The lotion of the present invention has the added benefit of being chemically and physically stable for at least 6 months at 40°C.

30

Fluticasone or a pharmaceutically acceptable salt or ester thereof, such as fluticasone propionate is added to the formulation in an amount of from about 0.005 to about 1.0 wt.% preferably 0.005 to 0.5 wt.%, and most preferably about 0.005 to about 0.1 wt.%.

35

The C<sub>14</sub>-C<sub>20</sub> fatty alcohol or mixtures thereof are added to the formulation as a thickener and stabilizer. Examples include, but are not limited to, cetyl alcohol, stearyl alcohol, and cetostearyl alcohol. The C<sub>14</sub>-C<sub>20</sub> fatty alcohol is present in an amount of

from about 1.0 to about 10.0 wt.%, preferably about 3.0 to about 7.0 wt.%, and most preferably about 4.0 to about 6.0 wt.%.

Conventional skin conditioning agents known in the art such as emollient skin

5 conditioning agents can be used in preparing the lotion of the present invention. Skin conditioning agents are defined in the CTFA (Cosmetic Toiletry and Fragrance Association) Cosmetic Ingredient Handbook (2nd ed. 1992) and the Handbook of Pharmaceutical Excipients (2nd ed. 1994). Examples of such skin conditioning agents include, but are not limited to cholesterol, glycerine, glycerol monostearate, isopropyl myristate and palmitate, and lanolin alcohols, or mixtures thereof. Particular examples are isopropyl myristate and cetostearyl alcohol. The skin conditioning agent is added in an amount of from about 1.0 to about 5.0 wt.%, preferably about 1.0 to about 3.0 wt.%, and most preferably about 1.0 to about 2.0 wt.%. In a preferred embodiment, 10 dimethicone is combined with at least one other skin conditioning agent, where the amount of dimethicone present is the formulation up to about 5.0 wt.%, preferably about 0.5 to about 3.0 wt.% and most preferably about 1.0 to about 2.0 wt.% of the 15 formulation.

Conventional surfactants used in the art of topical formulations for forming an oil-in-

20 water emulsion can be used and are not limited. Examples of such surfactants are polyoxyalkene oxides of C<sub>14</sub>-C<sub>20</sub> fatty alcohols and polyoxyalkylene sorbitan esters, or mixtures thereof with particular examples being Cetomacrogol® 1000 (Crodor Inc.), Ceteth-20®, Tween® 40 or Brig® 78. The surfactant is added in an amount of about 0.25 to about 3.0 wt.%, preferably about 0.5 to about 2.0 wt.%, and most preferably 25 about 0.75 to about 1.5 wt.%.

Mineral oil or white soft paraffin can be added to the lotion in small amounts to act as a skin conditioner. The lotion may contain no mineral oil or no white soft paraffin at all (0 wt.%) or up to about 10.0 wt.%, particularly up to about 5.0 wt.% and most preferably 30 up to about 2.0 wt.%.

Propylene glycol is added to the lotion formulation in an amount of from about 5.0 to about 15.0 wt.%, preferably about 7.0 to about 12.0 wt.% and most preferably 9.0 to 11.0 wt.%.

The viscosity of the topical lotion is from about 2,000 to about 17,000 cps, preferably about 3,000 to about 13,000 cps, as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

5 The pH range of the topical lotion should be from about 4 to 7. Preferred buffers to achieve this range, include, but are not limited to sodium citrate/citric acid, dibasic sodium phosphate/citric acid, and the like.

10 Preservatives used in the present invention can be any of those conventionally used in the art of topical formulations and preferably the formulation should pass US Pharmacopoeia, British Pharmacopoeia and European Pharmacopoeia standards. Preferred preservatives include, but are not limited to imidurea, methylparaben, propylparaben and the like.

15 Treatment with the lotion of the present invention is accomplished by applying the lotion to the affected areas to be treated. The treatment regimen is varied from patient to patient and condition to be treated and is usually applied once to twice a day. The lotion of the present invention is used to treat inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

20 The lotion of the present invention is manufactured in a conventional manner by mixing the ingredients at elevated temperatures (such as from 45-80°C) then cooling in order to achieve a smooth, homogeneous oil-in-water emulsion.

25 The following examples merely illustrate the lotion compositions of the invention and not to be construed as limiting. All weight percentages are weight percentages based on the total weight of the composition.

#### Examples

30 Example 1

A topical 0.05 wt.% fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		(w/w)
35	Cetostearyl alcohol, NF	5.00

	Isopropyl myristate, NF	1.00
	Dimethicone 360, NF	1.00
	Cetomacrogol 1000, BP	1.00
	Propylene glycol, USP	10.00
5	Imidurea, NF	0.30
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Citric acid (anhydrous), USP	.05
	Sodium citrate, USP	0.08
10	Purified water, USP	s

### Example 2

15 A topical 0.05 wt.% fluticasone propionate lotion formulation in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
	Cetostearyl alcohol, NF	5.25
	Isopropyl myristate, NF	2.00
	Propylene glycol, USP	0.00
20	Ceteth-20	0.75
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Citric Acid (anhydrous)	0.05
25	Dibasic sodium phosphate	0.06
	Purified water, USP	qs

### Example 3

30 A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
	Fluticasone Propionate	.05
	Cetostearyl Alcohol	5.0
35	Mineral Oil	3.0

5	Isopropyl myristate	3.0
	Ceteth-20	0.75
	Propylene Glycol	0.0
	Citric Acid (anhydrous)	0.05
	Dibasic Sodium Phosphate	0.06
	Imidurea	0.20
	Water	qs

Example 4

10

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
15	Fluticasone Propionate	.05
	Cetostearyl Alcohol	5.25
	Mineral Oil	1.0
	Isopropyl myristate	1.0
	Ceteth-20	0.75
	Propylene Glycol	10.0
20	Citric Acid (anhydrous)	0.05
	Dibasic Sodium Phosphate	0.06
	Imidurea	0.20
	Water	qs

25

Example 5

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
30	Fluticasone Propionate	.05
	Cetostearyl Alcohol	5.0
	Mineral Oil	10.0
	Isopropyl myristate	5.0
	Ceteth-20	0.75
35	Propylene Glycol	10.0

Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	qs

5

Example 6

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

10		<u>(w/w)</u>
	Fluticasone Propionate	.05
	Cetostearyl Alcohol	7.0
	Isopropyl myristate	2.5
	Dimethicone	2.5
15	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
	Citric Acid (anhydrous)	0.05
	Sodium Citrate	0.075
	Imidurea	0.30
20	Water	qs

Example 7

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

30		<u>(w/w)</u>
	Fluticasone Propionate	.05
	Cetostearyl Alcohol	7.0
	Isopropyl myristate	5.0
	Dimethicone	2.5
	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
	Citric Acid (anhydrous)	0.05
35	Sodium Citrate	0.075

Imidurea	0.30
Water	qs

Example 8

5

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
10	Fluticasone Propionate	.05
	Cetostearyl Alcohol	6.0
	Isopropyl myristate	2.0
	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
	Citric Acid (anhydrous)	0.05
15	Sodium Citrate	0.075
	Imidurea	0.30
	Water	qs

Example 9

20

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
25	Fluticasone Propionate	.05
	Cetostearyl Alcohol	4.7
	Isopropyl myristate	3.75
	Dimethicone	3.75
	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
30	Citric Acid (anhydrous)	0.05
	Sodium Citrate	0.075
	Imidurea	0.30
	Water	qs

Example 10

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
5	Fluticasone Propionate	.05
	Cetostearyl Alcohol	2.4
	Isopropyl myristate	2.5
	Dimethicone	5.0
10	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
	Citric Acid (anhydrous)	0.05
	Sodium Citrate	0.075
	Imidurea	0.30
15	Water	qs

Example 11

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
20	Fluticasone Propionate	.01
	Stearyl Alcohol	5.0
	Isopropyl myristate	3.0
	Dimethicone	3.0
25	Ceteth-20	0.75
	Propylene Glycol	5.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
30	Water	qs

Example 12

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
	Fluticasone Propionate	.01
	Stearyl Alcohol	2.5
	Mineral Oil	1.0
5	Isopropyl myristate	1.0
	Dimethicone	1.0
	Cetomacrogol 1000	0.5
	Propylene Glycol	15.0
	Imidurea, NF	0.20
10	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Water	qs

Example 13

15

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
	Fluticasone Propionate	0.1
20	Cetyl Alcohol	7.0
	Mineral Oil	2.0
	Isopropyl myristate	2.0
	Dimethicone	2.0
	Cetomacrogol 1000	1.5
25	Propylene Glycol	10.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Water	qs

30

Example 14

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

35

		<u>(w/w)</u>
	Fluticasone Propionate	0.1
	Stearyl Alcohol	7.0
	Mineral Oil	2.5
5	Dimethicone	2.5
	Ceteth-20	1.0
	Propylene Glycol	15.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
10	Propyl paraben, USP	0.10
	Water	qs

Example 15

15 A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
	Fluticasone Propionate	0.1
	Cetostearyl Alcohol	5.0
20	Mineral Oil	2.5
	Dimethicone	1.0
	Tween®40	0.5
	Propylene Glycol	10.0
	Imidurea, NF	0.20
25	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Water	qs

Example 16

30 A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
	Fluticasone Propionate	0.1
35	Stearyl Alcohol	5.25

	Mineral Oil	5.0
	Brig®78	2.0
	Propylene Glycol	5.0
	Imidurea, NF	0.20
5	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Water	qs

Example 17

10 A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
	Fluticasone Propionate	0.05
	Cetyl Alcohol	2.0
15	Isopropyl myristate	5.0
	Cetomacrogol 1000	0.5
	Propylene Glycol	10.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
20	Propyl paraben, USP	0.10
	Water	qs

Example 18

25 A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition:

		<u>(w/w)</u>
	Fluticasone Propionate	0.05
	Cetyl Alcohol	2.5
	Dimethicone	5.0
30	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
35	Water	qs

Experimental MethodVasoconstriction Study

5 The topical anti-inflammatory activity of fluticasone propionate formulations was measured using a vasoconstriction assay (McKenzie and Stoughton, Arch. Dermatol., 86, 608(1962)).

10 Approximately 0.1 mL of the drug product was placed on a 2 cm<sup>2</sup> area of the volar aspect of each volunteer's forearm. Application sites were protected with a guard to prevent removal or smearing, but were not occluded. After approximately 16 hours of contact, the protective guards were removed and the sites gently washed and dried. Skin vasoconstrictor evaluations were preformed on a 4 point scale (0 [no blanching]-3[marked blanching]) at time points corresponding to 2, 3, 6, 8, and 24 hours after drug removal. The data from this clinical trial were used to calculate the mean 15 blanching response and the area under the curve (AUC) for the blanching Versus time.

The higher the score, mean or area under the curve (AUC), the more topically potent:

Measure*	Lotion Example 1	Lotion Example 2	Cutivate® (Fluticasone propionate) Cream Comparative Example
AUC	28.4	26.7	21.4
Mean	1.58	1.49	1.22

20 \*Results from 17 volunteers.

The inventive lotions show higher vasoconstriction scores than fluticasone Cream. By looking at the 17 patient data set, the vasoconstriction potency of the inventive lotions over the cream is greater.

25

It will be apparent to those skilled in the art that many modifications thereof may be made without departing from the spirit and scope of the invention.

We claim:

1. A topical lotion which comprises:

(a) about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;

5 (b) about 1.0 to about 10.0 wt.% of a C<sub>14</sub>-C<sub>20</sub> fatty alcohol or mixtures thereof;

(c) about 1.0 to about 5.0 wt.% of one or more skin conditioning agents;

(d) about 5.0 to about 15.0 wt.% of propylene glycol; and

(e) up to about 10.0 wt.% of mineral oil or white soft paraffin.

10 2. A topical fluticasone lotion which comprises:

(a) fluticasone propionate in an amount of from about 0.005 to about 1.0 wt.%;

(b) a C<sub>14</sub>-C<sub>20</sub> fatty alcohol, or mixtures thereof, in an amount of from about 3.0 to about 7.0 wt.%;

(c) one or more skin conditioning agents in an amount of from about 0.5 to about

15 3.0 wt.%;

(d) a surfactant in an amount of about 0.25 to about 2.0 wt.%;

(e) propylene glycol in an amount of from about 7.0 to about 12.0 wt.%; and

(f) up to about 10 wt.% of mineral oil or white soft paraffin.

20 3. The lotion according to claim 1, further comprising up to about 5.0 wt.% dimethicone.

4. The lotion according to claim 2, further comprising up to about 5.0 wt.% dimethicone.

25

5. The lotion according to claim 1, wherein said pharmaceutically acceptable salt of fluticasone is fluticasone propionate.

6. The lotion according to claim 1, having the formula:

30	Fluticasone propionate	0.05 wt.%
	Cetostearyl alcohol	5.00 wt.%
	Isopropyl myristate	1.00 wt.%
	Dimethicone 360	1.00 wt.%
	Cetomacrogol 1000	1.00 wt.%
35	Propylene glycol	10.00 wt.%

	Imidurea	up to 0.30 wt.%
	Methyl paraben	up to 0.20 wt.%
	Propyl paraben	up to 0.10 wt.%
	Citric acid (anhydrous)	0.05 wt.%
5	Sodium citrate	0.08 wt.%
	Purified water	qs

7. The lotion according to claim 1, having the formula

	Fluticasone propionate	0.05 wt.%
10	Cetostearyl alcohol	5.25 wt.%
	Isopropyl myristate	2.00 wt.%
	Propylene glycol	10.00 wt.%
	Imidurea	0.20 wt.%
	Methyl paraben	0.20 wt.%
15	Propyl paraben	0.10 wt.%
	Purified water	qs

8. The lotion according to claim 1, having a viscosity of from about 2,000 to about 17,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm  
20 at 25°C.

9. The lotion according to claim 2, having the formula

	Cetostearyl alcohol	5.25 wt.%
	Isopropyl myristate	2.00 wt.%
25	Propylene glycol	10.00 wt.%
	Imidurea	0.20 wt.%
	Methyl paraben	0.20 wt.%
	Propyl paraben	0.10 wt.%
	Purified water	qs

30 10. The lotion according to claim 1, having a viscosity of from about 3,000 to about 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C

11. The lotion according to claim 2, having a viscosity of from about 3,000 to about 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.
- 5 12. The lotion according to claim 1, containing no mineral oil or white soft paraffin.
13. The lotion according to claim 2, containing no mineral oil or white soft paraffin.
- 10 14. A method of increasing the vasoconstrictor potency of fluticasone which comprises applying to the skin the lotion according to claim 1.
15. A method of increasing the vasoconstrictor potency of fluticasone propionate which comprises applying to the skin the lotion according to claim 2.
- 15 16. Use of the lotion according to claim 1 to increase the vasoconstrictor potency of fluticasone.
17. Use of the lotion according to claim 2 to increase the vasoconstrictor potency of fluticasone propionate.
- 20 18. A process for preparing a lotion according to claim 1, which comprises mixing the ingredients recited in claim 1 at elevated temperature; and then cooking said mixture.
- 25 19. A process for preparing a lotion according to claim 1, which comprises mixing the ingredients recited in claim 1 at elevated temperature; and then cooking said mixture.

ABSTRACT OF THE DISCLOSURE

5 The present invention is directed to a fluticasone lotion having improved vasoconstrictor activity. The fluticasone lotion exhibits high vasoconstrictor potency and excellent anti-inflammatory activity.

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